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| EXAMINER | |
|---|---|
| WANG, CHANG YU | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1649 | |

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/725,189 | LYNCH ET AL. | |
| | Examiner | Art Unit | |
| | Chang-Yu Wang | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *93-102,126-137,139-156 and 173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93-102,126-137,139-156 and 173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/13/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

## RESPONSE TO AMENDMENT

### *Status of Application/Amendments/claims*

Applicant's amendment filed September 13, 2006 is acknowledged. Claims 1-92, 103-125, 138, 157-172 are cancelled. Claims 93-102, 126-137, 139-156 and newly added claim 173 are pending and under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in the previous office action.

### *Oath/Declaration*

The request of a new Oath/declaration is withdrawn in response to Applicant's argument.

### *Claim Rejections/Objections Withdrawn*

The rejection of claims 152 and 153 under 35 U.S.C. 112, second paragraph as lacking clear antecedent bases for "the agent" is withdrawn in response to Applicant's arguments.

The rejection of claim 135 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to define what is encompassed within the claimed substrate is withdrawn in response to Applicant's arguments.

The rejection of claims 94-96 under 35 U.S.C. 112, second paragraph, as being indefinite because of recitations of analogs and derivatives is withdrawn in response to Applicant's arguments

The rejection of claim 139 under 35 U.S.C. 112, second paragraph, as being indefinite because of the recitation "modulate an activity" is withdrawn in response to Applicant's amendment to the claim.

The rejection of claims 94-102, 126-137 and 140-155 under 35 U.S.C. 112, second paragraph, as being indefinite as reciting "A" article is withdrawn in response to Applicant's amendment to the claims.

***Claim Rejections/Objections Maintained***

The objection to claims 95 and 155 as encompassing non-elected subject matter is maintained. Applicant argues that the office action of Mar 16, 2006 has not identified any prior art disclosing the elected species. Applicant also argues that if a generic claim is found allowable, the restriction requirement to the encompassed species should be withdrawn. Applicant's arguments have been fully considered but they are not persuasive. Levetiracetam (LEV) taught by Margineanu et al. as cited in the rejection under US35 § 103 is a N-alkylated 2-oxo-pyrrolidine derivatives (see p.1, 1st paragraph). The support can also be found in the reference of Shorvon et al. (see p.426, abstract, J. Neurol. Neurosur. Psych.2002. 72: 426-429). In addition, there is no generic claim is allowed. The objection to claims 95 and 155 as encompassing non-elected subject matter is maintained of record.

***Claim Rejections - 35 USC § 112***

The rejection of claims 93-102,126-137, and 139-156 under 35 U.S.C. 112, first paragraph because the specification does not enable the invention commensurate in scope with the claims is maintained for reasons of record in the previous office action. The rejection is also applied to new claim 173.

Applicant argues that the instant invention is based in part on the unexpected finding of the interaction of LEV with the SV2 protein to screen for a compound that would compete with the binding of LEV to an SV2 protein. Applicant argues that if the compound binds to an SV2 protein then it would also modulate the activity of an SV2 protein and would be useful for treating a neurological or endocrinological disease. Applicant argues that the specification teaches LEV and different LEV analogs and derivatives interacting with SV2 proteins. Applicant argues that the PTO fails to provide sufficient reasons to doubt that the claimed method can be used to identify compounds that bind and modulate an activity of an SV2 protein or compete with LEV or its analog or derivative for binding to the LBS and are useful in treating neurological or endocrniological diseases. Applicant argues that three SV2 proteins are highly homologous and are recognized by the same monoclonal anti-SV2 antibody as in the reference of Janz et al. (Neuroscience. 1999. 94: 1279-1290); thus Applicant states that the assays provided by the specification can be applied to the other SV2 proteins. Applicant argues that the claimed invention is based on the finding

of the activity of LEV (an antiepileptic drug) is mediated by SV2A as in Lynch et al. (PNAS. 2004. 101: 9861-9866). Applicant argues that LEV is an antiepileptic drug and Lynch et al. teach that there is a correlation between binding affinity of LEV or a LEV analog, such as ucb30889, to SV2A and anti-seizure potency of LEV derivatives in the audiogenic mouse model of epilepsy. Applicant further argues that US patent No. 6903130 and WO02/067931 have disclosed the use of pyrrolidones including LEV for the treatment of bipolar disorders, mania, migrane, chronic/neuropathic pain, hyperkinetic disorders such as Tourette syndrome, tics, and tremors; thus Applicant states that the instant specification enables the claimed method of using cell-free or membrane-free SV2 protein or fragment for identifying agents that interact with an SV2 protein or are useful for treating neurological or endocrinological diseases.

Applicant's arguments have been fully considered but they are not persuasive. Based on the specification, Applicant is enabling for identifying a compound that binds to an SV2 protein (SV2A/B/C) or a compound that competes with the binding of LEV to SV2A protein. In addition, Applicant is enabling for identifying LEV (an antiepileptic drug) that binds to SV2A and using LEV for treating epilepsy because LEV has been approved to be used in treating epilepsy. However, the claims are not limited to the full length SV2 proteins. The claims recite any SV2 fragment comprising LEV binding site (LBS) as in claims 93-102, 126-137. Although Applicant asserts that three SV2 proteins are highly homologous to each other and the finding in SV2A would also apply to the other SV2 proteins, it is noted that the activities and behaviors of currently identified

SV2A, SV2B, SV2C in response to different molecules are not the same. For example, botulinum neurotoxin A (BoNT/A) can interact with SV2C but not SV2A and SV2B, indicating the effect or response to BoNT/A is not same in these three SV2 proteins even they share high homology (Mahrhold et al. FEBS Lett. 2006. 580: 2011-4.). It suggests that the finding to one molecule (in this case SV2A) does not necessarily apply to other highly homologous molecules (in this case other SV2 proteins). Thus, it is unpredictable whether the results obtained from SV2A could be the same as in the other SV2 proteins. In addition, Applicant fails to teach what specific regions of the fragments comprise the LEV binding sites. Applicant fails to teach what amino acid sequence could be/not be included in the fragments in the claimed methods. Neither specification nor the prior art provide guidance as to enable one of skill in the art to use the fragment in a method to screen for the agent that could bind or compete with the binding of LEV to any SV2 protein, indicating that undue experimentation is required to practice the claimed invention. Further, claims 96 recite the limitation of competing with LEV or its analogs/derivatives in the claimed method. However, Applicant fails to teach whether other LEV analogs/derivatives are able to bind to any SV2 protein. Applicant only describes LEV L059, LEV analog ucb30889, ucb-101282-1 binding to the levetiracetam binding site of SV2A protein. It is unpredictable what other LEV analogs/derivatives are other than LEV L059, LEV analog ucb30889, ucb-101282-1 and whether they are able to bind to other SV2 proteins.

In addition, claim 93 as amended encompasses a method of identifying a compound in a cell free or membrane-free SV2 protein. However, claims 126-

131, 135-136 recite limitations that are required a measurement in a cell or plasma membrane system. Applicant fails to provide sufficient guidance as to how to measure divalent cations as in claims 126-129, SNARE complex formation as in claim 130, Ca channel assembly as in claim 131 and substrates across a membrane as in claims 135-136 without a cell or membrane system.

Furthermore, the claims also recite the limitation of identifying the compounds that are useful for treating any neurological disorders or endocrinological disorders as in claims 139-156 and 173. However, Applicant fails to teach whether other LEV analogs or derivatives could be used to treat epilepsy or other neurological/endocrinological disorders as recited in claims 139, 155, 156, and 173. The prior art and the specification have only taught that LEV can be used to treat epilepsy. However, neither prior art nor the specification teaches whether LEV or its analogs/derivatives could treat any neurological disorders/endocrinological disorders. The specification also fails to provide guidance as to how to use the test compounds that compete with LEV or other LEV analogs/derivatives in treating any neurological /endocrinological diseases. One of ordinary skill in the art cannot contemplate how to determine whether the test agents could be used in treating any neurological/endocrinological diseases, indicating undue experimentation is required. Thus, in view of the breadth of the claims, the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention. Therefore, the rejection of claims 93-

102,126-137, and 139-156 under 35 U.S.C. 112, first paragraph because the specification does not enable the invention commensurate in scope with the claims is maintained for reasons of record in the previous office action. The rejection is also applied to new claim 173.

The rejection of claims 93-102,126-137, and 139-156 under 35 U.S.C. 112, first paragraph, as failing to meet the written description requirement is maintained for reasons of record in the previous office action. The rejection is also applied to new claim 173 since the claim recites the same limitation as in original claims.

Applicant argues that the claims are directed to a method of identifying compounds that interacts with an SV2 protein but not directed to products of LEV analogs/derivatives. Applicant argues that the specification discloses several examples of LEV and alternative substitutions of LEV to obtain analogs/derivatives thereof. Applicant argues that the citation of Univ. of California v. Eli Lily & Co. and Vas-Cath Inc v. Mahurkar is not appropriate.

Applicant's arguments have been fully considered but they are not persuasive. In response to Applicant's argument that the citation of Univ. of California v. Eli Lily & Co. and Vas-Cath Inc v. Mahurkar is not appropriate, the examiner asserts that the citation is appropriate and applicable. Although the instant claims are directed to screening methods to identify compounds, the screening methods as recited in claims 96, 139-156 and 173 require identifying the screened compounds to compete with the binding site of LEV or its

analogs/derivatives on a SV2 protein as in claims 96, 139, 156. Claims 140-155 and 173 are dependent claims. However, Applicant fails to teach what other LEV analogs/derivatives are other than levetiracetam (LEV) L059, LEV analog ucb30889, ucb-101282-1 that were shown to bind to the SV2A protein. In addition, claims 93-102,126-137, and 139-156 recite a SV2 fragment comprising a LEV binding site. However, Applicant fails to teach what other specific common structures/regions/characteristics are other than LEV binding site. An ordinary skill in the art cannot contemplate what amino acid sequences are included/not included or what could be/not be changed in order to preserve the binding site of LEV. Further, claim 132 recites at least other protein, claim 135 recite at least one substrate, and claim 136 recites amines/other amino acids. However, Applicant fails to teach what other proteins, substrates, amines and amino acids are and can be used in the claimed invention. Thus, a skilled artisan cannot contemplate the functional relationship of the claimed genera of SV2 fragments, other proteins, substrates, amines and amino acids and the claimed invention. Therefore, the rejection of claims 93-102,126-137, 139-156 and 173 under 35 U.S.C. 112, first paragraph, as failing to meet the written description requirement is maintained.

The rejection of claims 93-102 and 139-156 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is maintained for reason of record in the previous office action. The rejection is

also applied to new claim 173 since the claim recites the same limitation as in original claims.

Applicant argues that the claims include all the essential steps for identifying compound/agent that interacts with an SV2 protein and the compound/agent may modulate any activity of an SV2 protein.

Applicant's arguments have been fully considered but they are not persuasive. The claims are directed to a method of identifying a compound/agent that binds to a SV2 protein. However, Applicant fails to include/teach a step as to how to measure/detect the effects of a test compound on any activity of SV2 since Applicant also fails to define what the other activities of SV2 are and how they can be evaluated and further to determine whether the test compound has any effect on any specific activity of SV2.

The rejection of claims 93, 130-132, 135, 137, and 139 under 35 U.S.C. 112, second paragraph, as being indefinite because of the recitation "modulate an activity" is maintained for reasons of record in the previous office action. The rejection is also applied to claims 126, 136.

Applicant argues that the word "modulate" is understood to include enhancement or inhibition of a function and Applicant intends to include both enhancement and inhibition of a function.

Applicant's arguments have been fully considered but they are not persuasive. Although the meaning of "modulate" is understood, Applicant fails to limit the activity of a SV2 protein. Thus, an ordinary skill in the art cannot

contemplate what to measure and how to evaluate the effect of a test compound in regulating any activity of a SV2 protein since the other activities of any SV2 protein are not known and it is also unclear how a SV2 is involved in vesicle exocytosis than its involvement of in a SNARE complex and binding to synaptotagmin and lamin-1.

***Obviousness-Type Non-Statutory Double Patenting***

The rejection of claims 93-102, 139-154 and 156 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 9-12,17-19, 22-25, 29,35, 37-40, 45-52, 54-57, 61-68, 71-74, and 78 of copending Application No. US/10/308,163 ('163), which has issued as US Patent No. 7090985 is maintained. The rejection is also applied to new claim 173 since the claim also recites the same limitation as in original claims.

Applicant argues that claims 1-4, 9-12, 17-19, 22-25,62-68, 71-74 and 78 of '163 (US 7090985) have been canceled. Applicant also argues that instant claims are directed to a method of identifying compounds/agents that interacts with SV2 protein using a cell-free/membrane-free SV2 protein or fragment thereof whereas claims 29, 35, 37-40, 45-52, 54-57 and 61 of '163 (US 7090985) are directed to a method of identifying a binding partner for an SV2A protein using recombinant host cells expressing an SV2A protein or fragment thereof.

Applicant's arguments have been fully considered but they are not found persuasive. Although the instant claims recite using a cell-free/membrane-free SV2 protein or fragment whereas the claims using a host cell expressing an

SV2A, it is noted that a method of screening for a compound using a cell-free/membrane-free polypeptide in a cell-free assay is a routine practice in the art for a high-throughput screening as evidenced by WO2003016475 (see p. 969-967). In addition, although the claims of '163 (US 7090985) recite identifying a binding partner for SV2A, the preferred species including identifying ucb 30889 at the SV2A levtiraetam binding site, which is the same species and anticipates the instant claims. In addition, instant claim 145 recites that SV2 is expressed on a transformed host cell. The rejection of claims 93-102, 139-154 and 156 the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29, 35, 37-40, 45-52, 54-57 and 61 of '163 (claims 1-24 of US Patent No. 7090985) is maintained of record until a terminal disclaimer is filed. It is noted that traversal at the time of indication of allowable subject matter will not be considered timely. The rejection is also applied to new claim 173.

***Claim Rejections - 35 USC § 102***

The rejection of claims 93, 97, 99, and 102 under 35 U.S.C. 102(a) as being anticipated by WO2003016475 (published Feb 27, 2003, effective filing date Aug 14, 2001.) is withdrawn. However, the rejection of claims 93, 97, 99, and 102 under 35 U.S.C. 102(e) as being anticipated by WO2003016475 is maintained.

Applicant argues that WO2003016475 does not anticipate the claims under 35 USC 102 (a) because the publication date of WO2003016475 is Feb 27, 2003 and the priority date of the instant is Dec 3, 2002. In addition, Applicant

argues that WO2003016475A2 does not teach screening assays using cell-free or membrane-bound free SV2 protein because the claimed method comprises a required step that obtaining cell-free or membrane-free SV2 protein prior to incubating the SV2 protein with the test compound.

Applicant's arguments have been fully considered but they are not persuasive. WO2003016475A2 does teach a cell-free assay using a cell-free/membrane bound free SV2 protein (see p. 969-967). WO2003016475A2 teaches biochemical and cell free assays that allow the identification of inhibitors and agonists of molecules that are involved in pain and suitable as lead structures for pharmacological drug development. Such assays involve contacting a form of a differentially expressed protein (e. g., full-length differentially expressed protein, a biologically active fragment of a differentially expressed protein, or a fusion protein comprising all or a portion of a differentially expressed protein) with a test compound and determining the ability of the test compound to act as an antagonist (preferably) or an agonist of the enzymatic activity of a differentially expressed protein as in claims 93, 97, 99, and 102 (see p. 969-967). In addition, WO2003016475A2 (PCT/US02/25765) is designated in US and published in English and the priority date is Aug 14, 2001, which is qualified as a 102 (e) reference. Thus, claims 93, 97, 99, and 102 are anticipated by WO2003016475.

***Claim Rejections - 35 USC § 103***

The rejection of claims 93-102 and 139-156 under 35 U.S.C. 103(a) as being unpatentable over WO2003016475 (published Feb 27, 2003, effective filing date Aug 14, 2001) in view of Margineanu et al. (Antiepileptic Drugs, 5th edition. Levy RH et al. 2002; Lippincott Williams & Wilkins, Philadelphia, PA. P.419-427, as cited in IDS submitted 09/23/04) and Berkower (Curr. Opi. Biotech. 1996.7:622-628) is maintained for reasons of record in the previous office action. The rejection is also applied to new claim 173 since the claim recite the same limitation as in original claims.

Applicant argues that WO2003016475 ('475) does not teach the use of cell-free or membrane-free SV2 protein in the screening assays. Applicant argues that neither Margineanu et al. nor Berkower et al. cure the deficiencies of '475 because the cited references do not teach or suggest obtaining cell-free or membrane-free SV2A protein or fragment thereof.

Applicant's arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under

35 U.S.C. 103. *Pro Mold Tool Col. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. MPEP. §2144.07. Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involve not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See *CTS Corp. v. Electro Materials Corp. of America* 202 USPQ 22 (DC SNY 1979); and *In re Burckel* 201 USPQ 67 (CCPA 1979). In considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to drawn therefrom. *In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). It is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In this case, WO2003016475 does teach a cell-free assay using a cell-free/membrane bound free SV2 protein as set forth above as in claims 93, 97, 99, and 102. Margineanu et al. teach that levetiracetam (LEV) (an anti-epilepsy drug approved by FDA) reduces the epilepsy induced by $GABA_A$ receptor antagonists (inhibitors for inhibitory neurotransmission) or NMDA

(neurotransmitters for excitatory neurotransmission) (see p. 422, second paragraph). In addition, the drugs inhibiting GABA-related convulsants and T-type $Ca^{++}$ channel can inhibit the binding of LEV to brain membranes as in claims 126-131, 135-137 (see p. 423, second column, first paragraph). Margineanu et al. further teach that LEV has effects on neurotransmitter receptors and neuron-ion channels and affects high-voltage $Ca^{++}$ currents, GABA-gated currents and AMPA-gated currents as in claims 126-129, 131, 136-137. The process of synaptic transmission is regulated by vesicle exocytosis, which is involved in SNARE complex formation and synaptic vesicles ducking on the plasma membrane as in claims 130, 132-135 (see p. 425, table 40.3 and p. 426, first column second paragraph). Berkower teaches that monoclonal antibodies are potent tools for diagnosis and disease treatment because they can have effects on immunosuppression, immunotherapy or blocking the interaction between receptor and ligands as in claim 98 (seep. 622, introduction). In addition, antibody fragments have better clearance rate and humanized antibodies can avoid the development and the adverse effects of human anti-mouse antibodies for patients as in claims 99-101 (see P. 626, Hybrid immunoglobulins). Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to be motivated and have expected success in screening for a compound or antibody that can compete with the levetiracetam binding site of SV2A for the potential treatment of neurological diseases associated with synaptic function by measuring the effects of levetiracetam on a synaptic activity that is regulated by excitatory (AMPA), inhibitory (GABA) synaptic transmission

and Ca channels since SV2A is involved in SNARE complex formation and exocytosis, and synaptic transmission is highly regulated by SNARE complex and vesicle fusion/exocytosis. In addition, since the humanized antibodies or antibody fragments have better effects on immunotherapy, it would be obvious for one of ordinary skill in the art to be motivated and have expected success in screening for humanized antibodies that compete with the levetiracetam-binding site of SV2A for treating epilepsy as taught by WO2003016475A2, Margineanu et al. and Berkower. Thus, the rejection of claims 93-102 and 139-156 under 35 U.S.C. 103(a) as being unpatentable over WO2003016475A2 in view of Margineanu et al. and Berkower is maintained.

The rejection of claims 93, 126-137 under 35 U.S.C. 103(a) as being unpatentable over WO2003016475A2 (published Feb 27, 2003, effective filing date Aug 14, 2001) in view of Xu et al. (Nat. Cell Biol. 2001, 3:691-698, as cited in IDS submitted 09/23/04) and Son et al. (J. Biol. Chem. 2000, 275: 451-460 as cited in IDS submitted 09/23/04) is maintained for reasons of record in the previous office action.

Applicant argues that WO2003016475 ('475) does not teach the use of cell-free or membrane-free SV2 protein in the screening assays. Applicant argues that neither Xu et al. nor Son et al. cure the deficiencies of '475 because the cited references do not teach or suggest obtaining cell-free or membrane-free SV2A protein or fragment thereof. In addition, Applicant argues that claims 139 and 156 require the addition of LEV or an analog or derivative thereof in the

screening assay for competition with the binding to the LBS on the SV2 protein but the cited references do not teach the interaction of LEV with SV2 proteins.

Applicant's arguments have been fully considered but they are not persuasive. '475 does teach a cell-free assay using cell-free or membrane-free SV2 as set forth above as in claims 93, 97, 99, and 102. Xu et al. teach that SV2A is a molecule involved in exocytosis and modulate the formation of SNARE complex for vesicle fusion by measuring the membrane capacitance and $Ca^{++}$ concentration as in claims 127-131 (see p. 692, figures 2 and 5). Xu et al. teach that SV2A modulates synaptic vesicle fusion and the interaction of SV2A with a synaptic protein, synaptotagmin, is $Ca^{++}$-dependent (see p. 696, discussion), which also affects the $Ca^{++}$ channel activity as in claims 130-133, 135-137. Son et al. teach that SV2A forms a complex with laminin-1 in synaptosomes through the direct binding to laminin-1 as in claim 134 (see p. 451, abstract). Thus, it would have been obvious for one of ordinary skill in the art at the time the instant invention was made to be motivated and have expected success in screening for a compound that binds to SV2A or screening for a compound or antibody that can compete with the levetiracetam binding site of SV2A by measuring the vesicle exocytosis, SNARE complex formation and $Ca^{++}$ channel activity since SV2A has been shown to be involved in formation of the SNARE complex for vesicle fusion and the interaction of SV2A with SNARE complex is through the interaction with synaptotagamin and laminin-1. In addition, $Ca^{++}$ is required for the process of exocytosis, which involves the cation influx/exflux and Ca++ channel activity.

In response to Applicant's argument that claims 139 and 156 require the addition of LEV to compete with the LBS site on SV2 protein, it is noted that claims 139 and 156 are not under this rejection. Thus, the rejection of claims 93, 126-137 under 35 U.S.C. 103(a) as being unpatentable over WO2003016475A2 (published Feb 27, 2003, effective filing date Aug 14, 2001) in view of Xu et al. (Nat. Cell Biol. 2001, 3:691-698, as cited in IDS submitted 09/23/04) and Son et al. (J. Biol. Chem. 2000, 275: 451-460 as cited in IDS submitted 09/23/04) is maintained.

***Conclusion***

NO CLAIM IS ALLOWED.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
November 13, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER